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EGFR and RB1 as dual biomarkers in HPV-negative head and neck cancer

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Abstract

© 2016 American Association for Cancer Research.Clinical decision making for human papillomavirus (HPV)-negative head and neck squamous cell carcinoma (HNSCC) is predominantly guided by disease stage and anatomic location, with few validated biomarkers. The epidermal growth factor receptor (EGFR) is an important therapeutic target, but its value in guiding therapeutic decision making remains ambiguous. We integrated analysis of clinically annotated tissue microarrays with analysis of data available through the TCGA, to investigate the idea that expression signatures involving EGFR, proteins regulating EGFR function, and core cell-cycle modulators might serve as prognostic or drug response-predictive biomarkers. This work suggests that consideration of the expression of NSDHL and proteins that regulate EGFR recycling in combination with EGFR provides a useful prognostic biomarker set. In addition, inactivation of the tumor suppressor retinoblastoma 1(RB1), reflected by CCND1/CDK6-inactivating phosphorylation of RB1 at T356, inversely correlated with expression of EGFR in patient HNSCC samples. Moreover, stratification of cases with high EGFR by expression levels of CCND1, CDK6, or the CCND1/CDK6-regulatory protein p16 (CDKN2A) identified groups with significant survival differences. To further explore the relationship between EGFR and RB1-associated cell-cycle activity, we evaluated simultaneous inhibition of RB1 phosphorylation with the CDK4/6 inhibitor palbociclib and of EGFR activity with lapatinib or afatinib. These drug combinations had synergistic inhibitory effects on the proliferation of HNSCC cells and strikingly limited ERK1/2 phosphorylation in contrast to either agent used alone. In summary, combinations of CDK and EGFR inhibitors may be particularly useful in EGFR and pT356RB1-expressing or CCND1/CDK6-overexpressing HPV-negative HNSCC.

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